IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

(Attorney Docket No. 01-660)

In re the Application of:		)
	Mohammad S. Nasir and Michael E. Jolley	)
		) Group Art Unit: 1641
Serial No.:	09/905,452	)
		) Examiner: Deborah A. Davis
Filed:	July 13, 2001	)
		) Confirmation No. 5761
For:	Fluorescence Polarization-Based Homogeneous Assay for Aflatoxins	)

REPLY BRIEF

(filed in response to the Examiner's Answer mailed May 21, 2007)

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I. Introduction

The Examiner's Answer mailed May 21, 2007 failed to rebut the points of clear error identified in Applicant's Appeal Brief. This Reply Brief addresses the specific arguments made in the Examiner's Answer.

II. Argument

A. The Examiner Erred in Rejecting Claims 1-4, 8, and 11-18 as Being Obvious over a Combination of Dixon and Nasir

In Section VII.A of the Appeal Brief, Applicant demonstrated that even if Dixon and Nasir were to be combined together, the resulting combination fails to teach or suggest all of the limitations recited in claims 1-4, 8, and 11-18. In particular, the Dixon/Nasir combination fails to teach or suggest either (i) a "tracer comprising an aflatoxin oxime conjugated to a fluorophore," as recited in independent claims 1 and 11; or (ii) "said tracer being able to bind to said antibody to produce a detectable change in fluorescence polarization," as recited in claims 1 and 11. The Examiner's Answer only reinforces the fact that the Dixon/Nasir combination fails to teach either of these elements.

With respect to element (i), the Examiner's Answer admits that the primary reference, Dixon, does not teach an aflatoxin oxime conjugated to a ***fluorophore*** label, because Dixon actually teaches an aflatoxin oxime conjugated to a ***protein*** label (horseradish peroxidise). Despite this admission, the Examiner inconsistently argues that Dixon's statement regarding conversion of aflatoxin to aflatoxin oxime for conjugation of two proteins, neither of which was used as a label, somehow applies to ***all*** labels, including fluorophores.

With respect to element (ii), the Examiner's Answer failed to point to any prior art teaching that an aflatoxin oxime conjugated to a fluorophore would have the special property of

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being able to bind to an antibody to produce a detectable change in fluorescence polarization. Instead, the Examiner argued that it would have been obvious that the tracer would overcome the obstacle of the "propeller effect" and have this special property because the inventor "overcame this obstacle." That argument, however, violates the rule that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." MPEP § 2143; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

1. The Examiner has admitted that Dixon does not teach an aflatoxin oxime conjugated to a fluorophore

Regarding Dixon, the primary reference in the Examiner's combination, the Examiner's Answer admitted (on page 9) that "the prior art reference does not teach an aflatoxin oxime conjugated to a fluorophore label." Instead, the Examiner acknowledged that Dixon teaches an aflatoxin oxime conjugated to a horseradish peroxidise label. *See* Examiner's Answer, pp. 7, 9. Thus, the Examiner has now recognized the difference between enzyme labels like horseradish peroxidise (proteins) and fluorophore labels. This difference is crucially important in the present case because Applicant's claims recite tracers that use ***fluorophore*** labels, whereas Dixon teaches a ***protein*** label.

Given Dixon's focus on protein labels, the Examiner's central argument regarding Dixon is fatally flawed, as discussed below.

2. Dixon does *not* disclose that aflatoxin must be converted to aflatoxin oxime in order to conjugate a fluorophore

The Examiner's Answer repeatedly argues that Dixon discloses that aflatoxin has to be converted to aflatoxin oxime before being conjugated to a "label." *See* Examiner's Answer, pp.

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7-9. The Examiner then applies this supposed teaching to Applicant's claims by arguing that aflatoxin would have to be converted to aflatoxin oxime before being conjugated to a fluorophore. The fatal flaw in this line of reasoning is that the "label" in Dixon is a protein (horseradish peroxidise), whereas the "label" in Applicant's claims is a fluorophore. Thus, the Examiner's argument uses the term "label" as a wiggle-word to try to bridge the gap between Dixon's disclosure and Applicant's claims.

In fact, Dixon does not teach anything about conjugating to "labels" generally, because Dixon teaches conjugating ***protein*** labels. As described on page 4 of Applicant's Appeal Brief, the only materials being conjugated to aflatoxin in Dixon are proteins, namely, horseradish peroxidise (HRP), bovine serum albumin (BSA), and ovalbumin (OA). Thus, Dixon's statement regarding conversion of aflatoxin to aflatoxin oxime for conjugation must be understood in the context of the specific conjugation that was actually done in Dixon, i.e., conjugation to proteins, not fluorophores. Indeed, the Examiner has admitted that Dixon "does not teach an aflatoxin oxime conjugated to a fluorophore label." *See* Examiner's Answer, p. 9.

Moreover, the statement in Dixon does not purport to refer to labels at all, but simply describes the procedure that was used to conjugate BSA and OA:

> Since aflatoxin B_1 possesses no reactive groups for conjugation, it was first converted to aflatoxin-B_1-carboxymethylamine (aflatoxin B_1-oxime) in the 1-position by the method of Chu, Hsia and Sun ... and then conjugated to BSA or OA (fraction VII) by the N-hydroxysuccinimide procedure of Kitagara et al ...

(col. 4, line 66 – col. 5, line 4). The Examiner's claim that this statement describes labelling is unsupported. Neither BSA nor OA was used as a label in Dixon's assays. Instead, as the Examiner has admitted, Dixon's label was HRP. *See* Examiner's Answer, p. 9. Thus, the statement does not describe Dixon's own HRP label, much less any other type of label.

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Given the foregoing, there is no basis for the Examiner's attempt to read Dixon's statement (which does not refer to labels at all) so broadly as to cover conjugation of every type of label under the sun, and certainly no basis for reading into this statement anything about conjugation of fluorophore labels. In addition, Nasir, the other reference in the Examiner's combination, actually teaches away from an aflatoxin oxime conjugated to a fluorophore. *See* Appeal Brief, pp. 6-7. Because neither Dixon nor Nasir teaches or suggests an aflatoxin oxime conjugated to a fluorophore, the Examiner has clearly erred in rejecting the pending claims.

3. The Examiner's rationale would improperly change the principle of operation in Dixon

In addition to Dixon's failure to teach anything about conjugating fluorophore labels to aflatoxin, Applicant has established that the Examiner's Dixon/Nasir combination would improperly change the principle of operation set forth in Dixon. *See* Appeal Brief, p. 5. In response, the Examiner has argued that "the modification of Dixon by Nasir would not change the principle of operation because both references are drawn to detection of toxins in grains. Therefore, the principle of operation appears to be the same." *See* Examiner's Answer, p. 8. However, detection of toxins in grains is the ***end result***, not the "principle of operation." The "principle of operation" refers to how the end result is achieved.

This distinction is well exemplified by the *Ratti* case discussed in MPEP § 2143.01(VI). In *Ratti*, the end result in both the claims and the prior art was an oil seal. However, the prior art and the claimed invention differed in the way the oil seals worked. The decision held that the combination of references did not make the claims obvious because the combination would require a substantial reconstruction and redesign of the elements shown in the primary reference

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as well as a change in the basic principle under which the primary reference construction was designed to operate. *See* MPEP § 2143.01(VI).

The Examiner's Dixon/Nasir combination suffers from the same problem. Dixon's HRP enzyme label is chemically and functionally very different from a fluorophore label. The HRP functions as a label by acting on a substrate (ABTS) in order to make the results of the assay visible (e.g., by measuring absorbance at 405 nm). In contrast, fluorophores work in a different way; they emit photons of light when they are excited with photons of suitable energy (Nasir, p. 178). In addition, Dixon's aflatoxin B_1-HRP conjugate is used in a heterogeneous assay, namely, a solid-phase ELISA assay (col. 6, lines 23-44). In contrast, the fluorophore of claims 1 and 11 is used in a homogenous assay.

These substantial differences between the HRP label in Dixon and the fluorophore label in the claimed invention make clear that the Examiner's combination would involve changing the basic principle of operation in Dixon. Thus, the Examiner has not established a *prima facie* case of obviousness.

4. The prior art does not teach a tracer, comprising an aflatoxin oxime conjugated to a fluorophore, being able to bind to an antibody specific for aflatoxin to produce a detectable change in fluorescence polarization

The Examiner has not identified any prior art teaching of a tracer, comprising an aflatoxin oxime conjugated to a fluorophore, that has the special property of being able to bind to an antibody specific to aflatoxin to produce a detectable change in fluorescence polarization, as recited in independent claims 1 and 11. Although the Examiner's Answer attempts to address this claim element, the Examiner's arguments are fraught with error.

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Dixon teaches an ELISA assay, not a fluorescence polarization assay. Nonetheless, the Examiner has argued that because both assays involve antibody binding, modifying Dixon to provide a fluorescence polarization assay would have had a reasonable expectation of success. *See* Examiner's Answer, p. 9. This argument is flawed for at least two reasons. First, the prior art actually teaches that "[i]n ELISA compounds adsorbed to the solid phase may have different affinities than in solution." *See* Nasir, p. 181, col. 2. Thus, the fact that binding occurred in Dixon's ELISA (heterogeneous) assay does not mean that binding would necessarily occur in a fluorescence polarization (homogeneous) assay. Second, and more importantly, a successful fluorescence polarization assay requires more than simply antibody binding; it requires a tracer that produces ***a detectable change in fluorescence polarization*** upon binding with the antibody. Since the Examiner has admitted that Dixon does not teach an aflatoxin oxime conjugated to a fluorophore, Dixon cannot possibly teach a tracer that has this special property.

The Examiner also argued that "Nasir taught using a Fluorescence Polarization assay method to label and detect a broad range of mycotoxins, which is a form of aflatoxins." *See* Examiner's Answer, p. 9. In fact, aflatoxins are a type of mycotoxin. However, though the Nasir reference includes a section regarding mycotoxins, Nasir makes no mention of the particular category of aflatoxins. *See* Nasir, pp. 181-182. This lack of mention is significant because mycotoxins "have a wide array of chemical structures." *See* Pestka, p. 120. Given this wide array of chemical structures, Nasir's general statements regarding mycotoxins do not suggest the successful application of the fluorescence polarization technique to aflatoxins specifically.

In any event, Nasir does not disclose the detection of a "broad range of mycotoxins" using fluorescence polarization, as the Examiner has suggested. What Nasir actually states is

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that fluorescence polarization "is a technique of great potential in this area of research." *See* Nasir, p. 182, col. 1. Thus, what Nasir actually taught was the need for further research. This is reinforced by the fact that Nasir did not report any results of any successful fluorescence polarization assay for any mycotoxin. Instead, Nasir referred to fluorescence polarization assays that were used to detect ***other*** substances (oleanderin, digitoxin, digoxin, pesticides, and herbicides). *See* Nasir, p. 182, col. 1. Therefore, in relying on Nasir's statements regarding mycotoxins, the Examiner is relying on an improper "obvious to try" rationale. *See* MPEP § 2145(X)(B), citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Perhaps most egregious of all is the Examiner's treatment of the "propeller effect." As described on pages 8-9 of the Appeal Brief, the Nasir reference describes a phenomenon called the "propeller effect," whereby "although binding has occurred, little polarization shift is observed." *See* Nasir, p. 180, col. 2. Thus, the prior art teaches that the "propeller effect" is an obstacle to developing a successful fluorescence polarization assay, but the prior art does not teach that an aflatoxin oxime conjugated to fluorophore would overcome this obstacle. The Examiner, however, dismissed the "propeller effect" as an obstacle to developing a fluorescence polarization assay because "Nasir overcame this obstacle." *See* Examiner's Answer, p. 10. However, the mere fact that the inventors found a solution does not mean that the solution was obvious: "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." MPEP § 2143; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The inventors' solution was not taught by the prior art. To the contrary, Nasir taught regarding the "propeller effect" problem that "[i]n order to attain the best results one must

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employ the shortest and most rigid linkage possible between the fluorophore and the ligand." *See* Nasir, p. 180, col. 2. By using an aflatoxin oxime instead of aflatoxin, the inventors went against this teaching. In particular, the addition of the oxime linkage went against the teaching of making the linkage between the fluorophore and the ligand as short and rigid as possible. The fact that the inventors' solution was contrary to the accepted wisdom in the art is evidence that the solution was nonobvious. *See* MPEP § 2145(X)(D)(3), citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

In the face of this evidence, it is clear that the Examiner has not shown any prior art teaching that an aflatoxin oxime conjugated to a fluorophore would have the special property of being able to bind to antibodies specific to aflatoxin to produce a detectable change in fluorescence polarization. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

B. The Examiner Erred in Rejecting Claims 5-7 as Being Obvious Over a Combination of Dixon, Nasir and Michel

Claims 5-7 depend from claim 1. As discussed above, the combination of Dixon and Nasir fails to teach or suggest all of the limitations of claim 1. Michel does not make up for the deficiencies in the Dixon/Nasir combination. Thus, the Examiner's rejections of claim 5-7 are improper for at least the same reasons that the Examiner's rejection of claim 1 is improper.

C. The Examiner Erred in Rejecting Claims 9-10 as Being Obvious Over a Combination of Dixon, Nasir and McMahon

Claims 9-10 depend from claim 1. As discussed above, the combination of Dixon and Nasir fails to teach or suggest all of the limitations of claim 1. McMahon does not make up for

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the deficiencies in the Dixon/Nasir combination. Thus, the Examiner's rejections of claim 5-7 are improper for at least the same reasons that the Examiner's rejection of claim 1 is improper.

III. Conclusion

Applicant has demonstrated that the rejections of claims 1-18 are in error as a matter of law. Applicant therefore requests reversal of the rejections and allowance of all pending claims in this application.

Respectfully submitted,

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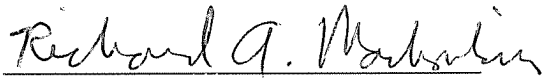
Date: July 20, 2007

By: 

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